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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,307	07/25/2003	Jan G.J. van de Winkel	MXI-101CPACN	1910

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EXAMINER
VANDERVEGT, FRANCOIS P

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,307	VAN DE WINKEL, JAN G.J.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20040830.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of U.S. Application Serial Number 09,251,570; wich claims the benefit of the filing date of provisional application 60/074,967.

Claims 1-20 are currently pending and are the subject of examination in the present Office Action.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 3-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a first agent that does not bind in an Fc dependent manner to an Fc receptor on a macrophage, does not reasonably provide enablement for the full scope of "a first agent which binds to an Fc receptor at a site which is distinct from that bound by endogenous immunoglobulins." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to the use of "a first agent which binds to an Fc receptor at a site which is distinct from that bound by endogenous immunoglobulins." However, other than the actual binding of immunoglobulin Fc domain to an Fc receptor, the specification does not disclose any other endogenous immunoglobulin binding to Fc receptor that is excluded. For example, it has been established that in some autoimmune diseases, such as systemic lupus erythematosus and Sjögren syndrome, autoantibodies to Fc receptors are generated in some patients (see, e.g., Deo et al (Immunol. Today [3/1997] 18(3):127-135; C5 on form PTO-1449), page 133, column 2,for example). However, the specification does not disclose the binding site of any of these antibodies to the Fc receptor. In fact, it is

likely that it would be outside the realm of routine experimentation to determine all the sites that these endogenous autoantibodies bind to. For example, in myasthenia gravis it has been established that about 60-70% of the autoantibodies that bind to the nicotinic acetylcholine receptor (AChR) bind to a domain on the alpha subunit known as the "main immunogenic region" (MIR). However, even this MIR-directed population is heterologous, recognizing multiple epitopes within the MIR (page 2343, column 2 of Tzartos et al. (J. Immunol. [1985] 134(4):2343-2349; U on form PTO-892) for example). Furthermore, this leaves 30-40% of those endogenous anti-AChR to bind to undetermined immunoepitopes.

Based upon the lack of guidance in the specification, the unpredictability of the art regarding exactly which epitopes of the Fc receptor would be bound in an antigen-specific manner, the limited nature of the working examples in the specification and the nature of the invention, it would require an undue amount of experimentation on the part of one skilled in the art to identify the full scope of sites on the Fc receptor that are distinct from sites that are bound by endogenous immunoglobulins because it would be impossible to identify all the sites that are potentially bound by endogenous immunoglobulins.

3. Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The hybridoma cell lines producing the antibodies "mab 22, 32, 197 and H22" are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of *35 U.S.C. 112*, first paragraph, may be satisfied by a deposit of said cell lines. *See 37 C.F.R. 1.802.*

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. *See 37 C.F.R. 1.808.*

If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a

statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

In addition, the identifying information set forth in *37 C.F.R. 1.809 (d)* should be present in the specification. *See 37 C.F.R. 1.803-1.809* for additional explanation of these requirements.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from Applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the Applicant's possession at the time the application was filed.

Applicant's attention is directed to *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985), and 37 C.F.R. 1.801-1.809 for further information concerning deposit practice. See MPEP 1.804(b).

It is noted that the antibodies have been deposited with the ATCC (paragraph bridging pages 10-11 of the specification), however the terms of the deposit are not disclosed and the address of the depository is not included.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is ambiguous and unclear in the recitation of "a first agent which binds to an Fc receptor at a site which is distinct from that bound by endogenous immunoglobulins." Is the claim referring only to the binding of the Fc domain of an immunoglobulin to the receptor or is the recitation inclusive of antibodies, such as an autoantibody or a polyreactive antibody, which may bind to the Fc receptor in an antigen-specific manner? Applicant should clarify the meaning of the recitation.

Claim 10 is ambiguous and unclear in its recitation of "mab 22, 32 and 197" by only their laboratory names in the claim. The same designations may likely to be used by others as well to designate different antibodies. It is suggested that the corresponding accession or deposit numbers from an acceptable depository be recited in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-10, 12, 13, and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,635,600 to Fanger et al. (A4 on form PTO-1449) in view of U.S. Patent No. 5,922,845 to Deo et al (A on form PTO-892).

The claims are drawn to selectively reducing the number or actyivity of macrophages by administering a compound comprising a first agent that binds to the Fc receptor on a macrophage and a second agent that kills or reduces the activity of the macrophage. The claims further recite that the first agent does not bind to the same site as that bound by endogenous immunoglobulin. This recitation is being interpreted here as meaning that the first agent does not bind to the region of the Fc receptor that is responsible for binding to the Fc domain of an immunoglobulin.

The '600 patent teaches the use of a compound comprising a first agent that is an anti-Fc.gamma.R antibody (see entire disclosure, Abstract in particular) and a second agent that is a toxin, such as ricin (column 7, lines 3-10 in particular). The '600 patent teaches that the first agent can be a monoclonal antibody selected a group comprising mAbs 22, 32 and 197 (column 5, lines 12-16 in particular). The '600 patent teaches that the anti-FcR antibodies do not interfere with the binding of IgG to the Fc receptor (column 2, lines 15-24 in particular). The '600 patent teaches that this compound can be used to reduce the number of Fc receptors on the surface of a macrophage, thereby reducing the ability of the macrophage to clear antibody-coated self cells in a subject with rheumatoid arthritis (column 7, lines 32-40 in particular). The '600 patent teaches that the second agent can be a liposome containing anticancer drugs to kill macrophages in some hematological cancers (column 6, lines 58-65 in particular).

The '600 patent does not teach topical, subcutaneous or intradermal administration.

The '845 patent teaches that antibodies that bind to Fc receptors on macrophages can be administered subcutaneously (column 16, lines 14-33 in particular) or intradermally (column 21, lines 35-43 in particular).

The '600 patent does not teach first agent that is directed to Fc.alpha. receptors [claim 7].

The '845 patent teaches that macrophages can also be modulated using antibodies directed to Fc.alpha. receptors and that these anti- Fc.alpha. receptor antibodies do not interfere with Fc-mediated

binding of endogenous IgA (see entire disclosure, column 1, lines 46-51 in particular). the '845 patent additionally teaches that the anti-FcR antibody can be a single chain antibody (column 2, lines 3-25 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of the '600 and '845 patents. One would have been motivated to combine the teachings, with a reasonable expectation of success, because both teach the value of modulating the activity of macrophages for the treatment of certain conditions and by the teaching of the '845 patent that the compound can be applied locally via subcutaneous or intradermal means.

Conclusion

3. No claim is allowed.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
June 22, 2006

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT 182